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**OCT 05 2006**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Serial No. 10/677,733

Customer No.: 23379

Applicant: Gardner et al.

Confirmation No. 4887

Filed: Oct 01, 2003

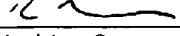
Group Art Unit: 1656

Docket No. UTSD:1510

Examiner: Nashed, Nashaat T.

Title: NMR Detection of Foreign PAS  
Domain Ligands

**CERTIFICATE OF TRANSMISSION**  
I hereby certify that this corr is being transmitted by facsimile to the  
Comm for Patents at 571-273-8300 on October 5, 2006.

Signature   
Richard Aron Osman

**BRIEF ON APPEAL**

The Honorable Board of Appeals and Interferences  
United States Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Honorable Board:

We appeal from the Examiner's Sep 05, 2006 final rejection of claims 1 & 2.

**REAL PARTY IN INTEREST**

The real party in interest is the Board of Regents, the University of Texas System, the assignee of this application.

**RELATED APPEALS AND INTERFERENCES**

Appellants are unaware of any related appeals or interferences.

**STATUS OF CLAIMS**

Claims 1 & 2 are rejected and subject to this appeal.

## STATUS OF AMENDMENTS

All Amendments are believed to be properly before the Board.

## SUMMARY OF CLAIMED SUBJECT MATTER

A method of detecting binding of a PAS (Pcr-ARNT-Sim) domain with a foreign core ligand of the PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of: (a) detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand; and (b) comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain. Specification, p.2, line 25 – p.3, line 1; claim 1.

In a particular embodiment, the PAS domain is the PAS A domain of PAS kinase. Specification, p.3, lines 1-2; claim 2.

## GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIMS 1 & 2 UNDER 35USC112, SECOND PARAGRAPH.
  
1. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIMS 1 & 2 UNDER 35USC103(a).

## ARGUMENT

1. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIMS 1 & 2 UNDER 35USC112, SECOND PARAGRAPH

The claims are definite to one skilled in the art, as detailed below and documented in the expert Declaration of record.

- (a) A foreign ligand of a PAS domain is distinct from a natural ligand naturally associated

with the PAS domain in its host. This is consistent with our Specification which defines the foreign ligand as "not a natural ligand of the PAS domain" (e.g. p.4, lines 22-23) and "foreign to the [PAS domain] host." (e.g. p.5, line 24). One skilled in the art can discern what is, and what is not, a foreign ligand of a PAS domain, recognizes the term "foreign ligand" of a PAS domain as definite, and recognizes its metes and bounds.

To the extent the Action is construed to object to the term "PAS domains", we reiterate that PAS domains are one of the most well-studied and documented protein domains, subject to thousands of scholarly publications. The Specification teaches and exemplifies the claimed methods with a wide variety of suitable PAS domains including PAS kinase PAS A, NPAS2 PAS A, HIF2a PAS B, HIF1a PASB, ARNT PAS B and HERG terminal PAS (p.6, lines 3-5; p.14, line 8 - p.21, line 10). Those skilled in the art recognize in the Specification a description of the claimed method of detecting binding of a PAS domain with a foreign core ligand. The practitioner does not require a description of the atomic structure or amino acid sequence of every or any targeted PAS domain to practice the invention.

(b) The claims require that the recited PAS domain "comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity." This clause is literally self-explanatory to one skilled in the art, meaning literally that the core has no NMR-apparent a priori ("before experience") formed ligand cavity. This clause distinguishes and excludes those cores that have an NMR-apparent a priori formed ligand cavity. One skilled in the art can discern what is, and what is not, an "NMR-apparent a priori formed ligand cavity of a PAS domain hydrophobic core", recognizes the clause as definite, and recognizes its metes and bounds.

(d) The claims require comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain. This step is literally self-explanatory to one skilled in the art, requiring literally that the practitioner compare the first NMR spectrum (in the presence of the ligand) with the second NMR spectrum of the PAS domain (in the absence of the ligand) to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain. The step literally requires that the practitioner compare the NMR spectra to infer the presence of specific ligand binding. Details and examples of how the practitioner infers

the presence of specific ligand binding from compared NMR spectra are provided, *inter alia*, at p.13, line 29 - p.21, line 10. In the context of our disclosure, one skilled in the art can readily discern what it means "to infer the presence of the ligand specifically bound", recognizes the phrase as definite, and recognizes its metes and bounds.

II. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIMS 1 & 2 UNDER 35USC103(a).

Fesik (WO97/18471) discloses the use of particular two-dimensional  $^{15}\text{N}/^1\text{H}$  NMR correlation spectra to identify ligands of target biomolecules. Fesik teaches nothing about PAS domains.

Edery (US 5,843,683) characterizes four PAS domain containing proteins (AHR, SIM, ARNT and PER) and use co-immunoprecipitation experiments to propose that PAS domains engage in PAS-PAS interactions. Edery proposes and claims assays for molecules that modulate PAS-PAS interactions.

Takahashi (US 6,291,429) describes circadian clock genes from humans and mice, and proposes contemplated uses of CLOCK polypeptides including use "in a screening assay for the identification of drugs or compounds that inhibit the action of CLOCK polypeptide (e.g., DNA binding)." Takahashi, col.9, lines 13-27.

Berkenstam (US 6,436,654) discloses and claims methods for identifying compounds which modulate the function of a functional domain of a variant of human HIF-1.alpha that lacks at least one functional domain thereof.

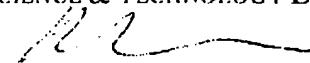
Our claims are specifically directed to a method of detecting binding of a PAS domain with a foreign core ligand of the PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity. The method specifically requires the steps of: (a) detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand; and (b) comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain.

As explained in our Specification some members of the PAS family are known to contain small molecule cofactors within their cores, and these cofactors are reportedly required for proper folding and functioning of the PAS domain within the context of the holo-protein. Specification, p.1, line 22 - p.2, line 1. However, for most PAS domains there is no evidence for such a cofactor. In fact, structurally characterized PAS domains without bound cofactors (Amezcu et al., 2002; Erbel et al., 2003; Morais Cabral et al., 1998) show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site. Specification, p.2, lines 2-5. Since the prior work provided no evidence of cofactors for most PAS domains, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have suspected that such PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding; in fact, the art (*supra*) teaches squarely away from such use.

Though the cited art does not support a *prima facie* case for obviousness, for good measure we have of record affirmative evidence documenting the fact that one skilled in the art would have considered the claimed invention nonobvious at the time it was made (attached expert Declaration).

Appellants respectfully request reversal of the pending Final Action by the Board of Appeals. The appeal brief fee is provided in the accompanying PTO-2038.

Respectfully submitted,  
SCIENCE & TECHNOLOGY LAW GROUP

  
Richard Aron Osman, J.D., Ph.D., Reg. No.36,627  
Tel (949) 218-1757; Fax (949) 218-1767

## CLAIMS APPENDIX

1. A method of detecting binding of a PAS (Per-ARNT-Sim) domain with a foreign core ligand of the PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:

detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand;  
and

comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain.

2. A method according to claim 1, wherein the PAS domain is the PAS A domain of PAS kinase.

EVIDENCE APPENDIX

132 Declaration of Professor Stephen R. Sprang dated Jun 19, 2006 (follows).

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DECLARATION UNDER 37CFR1.132

I, Professor Stephen R. Sprang, declare and state as follows:

1. I am a Professor in the Department of Biochemistry at the University of Texas Southwestern Medical School. The Board of Regents of the University of Texas System is the assignee of this patent application. I have authored numerous scientific papers in the field of protein regulation, and I am familiar with this patent application. A copy of my curriculum vitae is attached.

2. PAS domains are one of the most well-studied and documented protein domains, subject to hundreds of scholarly publications. The Specification teaches and exemplifies the claimed methods with a wide variety of suitable PAS domains including PAS kinase PAS A, NPAS2 PAS A, HIF2 $\alpha$  PAS B, HIF1 $\alpha$  PASB, ARNT PAS B and HERG N-terminal PAS domain (p.6, lines 3-5; p.14, line 8 - p.21, line 10). Those skilled in the art recognize in the Specification a description of the claimed method of detecting binding of a PAS domain with a foreign small molecule ligand that binds into the core of these domains. The practitioner does not require a description of the atomic structure or amino acid sequence of every or any targeted PAS domain to practice the invention.

3. While there is sequence variability across disparate PAS domains, those skilled in the art appreciate what is, and what is not a PAS domain, recognize the term PAS domain as definite, and recognize its metes and bounds. Indeed, the presence of PAS domains within a protein sequence can be identified using several computational methods that are publically available.

A foreign ligand of a PAS domain is distinct from a natural ligand naturally associated with the PAS domain in its host. This is consistent with the Specification which defines the foreign ligand as "not a natural ligand of the PAS domain" (e.g. p.4, lines 22-23) and "foreign to the [PAS domain] host." (e.g. p.5, line 24). One skilled in the art can discern what is, and what is not, a foreign ligand of a PAS domain, recognizes the term foreign ligand of a PAS domain as definite, and recognizes its metes and bounds.

The claims require that the recited PAS domain comprises a hydrophobic core that has no

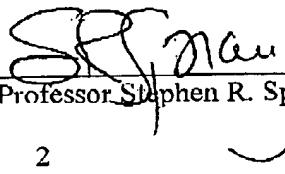
NMR-apparent a priori formed ligand cavity. This clause is literally self-explanatory to one skilled in the art, meaning literally that the core has no NMR-apparent a priori ("before experience") formed ligand cavity. This clause distinguishes and excludes those cores that have an NMR-apparent a priori formed ligand cavity. One skilled in the art can discern what is, and what is not, an NMR-apparent a priori formed ligand cavity of a PAS domain hydrophobic core, recognizes the clause as definite, and recognizes its metes and bounds.

The claims require comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain. This step is literally self-explanatory to one skilled in the art, requiring literally that the practitioner compare the first NMR spectrum (in the presence of the ligand) with the second NMR spectrum of the PAS domain (in the absence of the ligand) to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain. The step literally requires that the practitioner compare the NMR spectra to infer the presence of specific ligand binding. Details and examples of how the practitioner infers the presence of specific ligand binding from compared NMR spectra are provided, *inter alia*, at p.13, line 29 - p.21, line 10. In the context of the disclosure, one skilled in the art can readily discern what it means to infer the presence of the ligand specifically bound, recognizes the phrase as definite, and recognizes its metes and bounds.

4. As explained in the Specification some members of the PAS family are known to contain small molecule cofactors within their cores, and these cofactors are reportedly required for proper folding and functioning of the PAS domain within the context of the holo-protein. Specification, p.1, line 22 - p.2, line 1. However, for the vast majority of PAS domains there is no evidence for such a cofactor. In fact, structurally characterized PAS domains without bound cofactors (Amezcu et al., 2002; Erbcl et al., 2003; Morais Cabral et al., 1998) show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site. Specification, p.2, lines 2-5. Since the prior work provided no evidence of cofactors for most PAS domains, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have expected that such PAS domains would be rational candidates to screen for core ligand binding; in fact, the art (*supra*) teaches squarely away from such use. In my opinion one skilled in the art would have considered the claimed invention nonobvious at the time it was made.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application and any patent issuing therefrom.

Date: June 19, 2006

  
Professor Stephen R. Sprang

RELATED PROCEEDINGS APPENDIX

No related proceedings are known to exist.